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### **REMARKS**

Claims 287-291 were previously pending in this application. In the complete listing of claims above, claims 288 and 291 have been amended. New claims 292-307 have been added. No claims have been canceled by this paper. Accordingly, claims 287-307 are presented for further examination.

#### **Changes to the Claims**

As just indicated, claims 288 and 291 have been amended. In claim 288, two changes have been effected. First, this claim has been rewritten in independent form. Previously, claim 288 depended from claim 287. Second, a minor change (capitalizing "second dye") has been made. In claim 291, the term "heterodimeric dye" has been inserted before "composition" in the preamble in order to conform this claim with the other dependent claims (289 and 290).

New claims 292-307 have also been added. Claims 292 and 293 are directed to a rigid linker arm in the heterodimeric dye composition. Claim 292 recites that "said Second Dye is attached to said structure through a rigid linker arm." Claim 293 further defines the rigid linker arm as comprising "one or more peptide bonds." Support for the rigid linker arm concept and the subject matter of new claims 292 and 293 is found in the specification, for example, in the section titled "Rigid Linker Arms," beginning on page 39. See particularly, page 42, first two lines ("Examples of linear polar rigid units that would be useful in the present invention can include but not be limited to moieties comprising peptide bonds." (emphasis added)).

Claim 293 recites that the heterodimeric dye composition comprises "a bromine or chlorine counter-ion." Support is drawn, for example, from the bottom of Figure 9 [(7)  $R' = \text{NO}_2$ ,  $X = \text{Br}$  and (8)  $R' = \text{NH}_2$ ,  $X = \text{Cl}$ ] (emphasis added).

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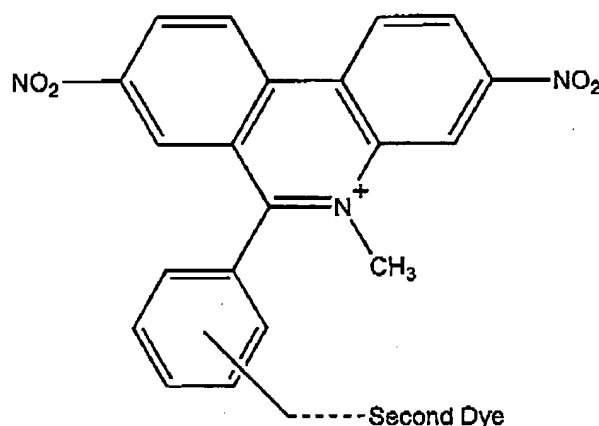
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Claims 295-296 mimic the language of claims 292-293, except that the former depend from claim 287. Claims 297-299 follow the language of claims 289-291, except that the former also depend from claim 287. Claim 300 depends from claim 287 and recites that the composition further comprises "a bromine or chlorine counter-ion" (same as claim 294).

In claim 301, Applicants are presenting another independent claim for the purpose of claiming a heterodimeric dye composition having the structure



wherein the Second Dye is not a phenanthridinium moiety. Support for claim 301 is again taken from the bottom of Figure 9 [(7)  $R' = NO_2$ ,  $X = Br$  and (8)  $R' = NH_2$ ,  $X = Cl$ ] (emphasis added).

The rest of the new claims, 302-307 adopt the language either of other previously presented claims or the new claims just discussed. Claims 302 and 303 refer to ring positions, just as in the case of claims 289-290. Claim 304 recites the members for the second dye, just as in claim 299. Claim 305-306 are directed to the rigid linker arm, just as in claims 292-293, respectively. Finally, claim 307 recites the heterodimeric dye composition as further comprising "a bromine or chlorine counter-ion."

It is believed that the foregoing amendments and new claims comprise subject matter to which Applicants are entitled to claims and that the subject matter does not insert new matter into Applicants' disclosure.

Entry of the above amendments and new claims is respectfully requested.

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### **Commonality of Ownership**

Applicants affirm that the subject matter of the various claims was commonly owned at the time their invention was made.

### **The First Rejection Under 35 USC §103(a)**

Claims 287-291 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Glazer et al. (U.S. Patent No. 5,646,264) in view of Lee et al. ["DNA sequencing with dye-labeled terminators and T7 DNA polymerase: effect of dyes and dNTPs on incorporation of dye-terminators and probability analysis of termination fragments," Nucleic Acids Research 20:2471-2483 (1992)]. In the July 13, 2005 Office Action (pages 2-3), it is stated:

Glazer discloses in Figure 4 the synthesis a heterodimeric dye composition comprising a first dye that comprises a phenanthridinium moiety and a second dye that is different from the first dye.

Glazer does not show that the attachment is through the phenyl ring.

Lee et al. disclose heterodimeric dye where the attachment is through a phenyl ring in ortho, meta or para position. See col. 6 , Tables 1-5.

Therefore it would have been obvious at the time the invention was made to synthesis heterodimeric dyes as taught by Glazer comprising an attachment via the phenyl ring as shown by Lee. The motivation is that the attachment is provided on a ring that is less steric and also viewed as an electrophilic moiety and more reactive toward nucleophilic moiety. It is well known in the art of organic chemistry that a phenyl ring comprising an electron withdrawing moiety such as the phenanthridinium moiety will be more reactive toward nucleophilic group and therefore can be substituted in ortho, meta or para position.

The obviousness rejection is respectfully traversed.

At the outset, Applicants respectfully point out that according to their originally filed disclosure

[I]t was a surprising and unexpected result that when meta-

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EthD was used in a different manner than the standard format, a greatly enhanced discrimination between bound and unbound was observed. The present invention discloses that when two ethidium bromide molecules are joined together through their phenyl groups, excitation at a wavelength below 400 nm can result in an increase of over 150 fold in fluorescent emission upon the binding of DNA to the homodimer as opposed to the 6 fold increase seen when the samples are excited at 493 nm.

Two other homodimeric ethidium bromide compounds (EthD-1 and EthD-2) are commercially available from Molecular Probes, Inc. (Eugene, OR). However, in contrast to the results with *meta*-EthD, the discrimination between bound and unbound dye was not substantially changed by exciting at wavelengths below 400nm. It should be pointed out that although *meta*-EthD, EthD-1 and EthD-2 are all ethidium bromide dimers, they are chemically dissimilar. As shown in (Figure 2), *meta*-EthD is comprised of two phenanthridinium rings linked together through the *meta* position of the phenyl rings through amide bonds. In contrast, the phenanthridinium rings of EthD-1 and EthD-2 dimers are joined together through the nitrogen of the center rings rather than through the phenyl rings. The intervening chain is comprised of an alkyl chain with two amine attachment groups which are secondary in EthD-1 and methylated to give the quaternary salts for EthD-2. The inability of the EthD-1 and EthD-2 compounds to exhibit the same results seen with *meta*-EthD demonstrates that the method of the present invention was not a predictable property of ethidium dimers per se.

In reading Applicants' above-quoted disclosure, it is apparent that switching from the traditional position of the nitrogen in the fused ring portion of the phenanthridinium to the phenyl ring position of phenanthridinium resulted in new and unexpected properties. Applicants did so and in so doing, obtained their unexpected results. It would not have been obvious to a person of ordinary skill in the art at the time of the present invention to choose the phenyl ring position over the traditional position (nitrogen of the fused ring portion), as used, for example, in EthD-1, EthD-2 and Glazer et al. Simply put, such a person would not have expected to obtain the unique and unexpected properties endowed by using the phenyl ring position as demonstrated by Applicants.

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In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the sole rejection of record.

Early and favorable action is respectfully requested.

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### **SUMMARY AND CONCLUSIONS**

In the claim listing above, claims 287-307 are presented for further examination. Of these, claims 288 and 291 have been amended and new claims 292-307 have been added.

The fee for adding new claims 292-307 is \$25 based upon the presentation of 21 total claims. This paper is also accompanied by a Request For Extension Of Time (Three Months) and authorization for the small entity fee therefor. No other fee or fees are believed due in connection with this paper. In the event that any fee or fees are due, however, the Patent and Trademark Office is hereby authorized to charge any such fee or fees to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,



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